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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/725,752	05/22/2001	Katsushi Tokunaga	2000-1639A	1603

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EXAMINER
JOHANNSEN, DIANA B

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/725,752	TOKUNAGA ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1-9, 12-13, and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *02/2001* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Preliminary Amendment filed May 22, 2001 and the paper and computer readable forms of the Sequence Listing filed July 23, 2001 have been entered.

2. It is noted that the instant application was filed November 30, 2000 in a language other than English. In accordance with 37 CFR 1.52, applicant has provided an English translation of the non-English language application, a statement that the translation is accurate, and the required processing fee. Accordingly, the filing date of the instant application is November 30, 2000.

Election/Restriction

3. Applicant's election without traverse of Group III, claims 10-11 and 14, in the Response filed February 10, 2003 is acknowledged. Applicant's election of the species FLICE inhibitory protein is also acknowledged. However, upon further consideration, the requirement to elect a single species is withdrawn with respect to elected Group III.

4. Claims 1-9, 12-13, and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the Response filed February 10, 2003.

Information Disclosure Statement

5. Regarding reference "AN" of the Information Disclosure Statement filed February 28, 2001, it is noted that the examiner has cited the date that the poster was presented and has indicated on the 1449 provided herewith that the English translation of the poster (which was provided in the IDS) was considered.

Specification

6. The use of the trademarks KLENTAQ®, AMPLITAQ GOLD®, and GENEAMP® has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

7. The title of the invention is not descriptive of the subject matter of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Method for diagnosis of Crohn's disease.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 10-11 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing Crohn's disease in which increased expression of at least one of the genes of claim 10 in a colon tissue sample or ileum tissue sample of a human patient is detected as an indicator of Crohn's disease, does not reasonably provide enablement for methods in which the expression of at least one of the genes of claim 10 is "analyzed" in any type of biological sample from any "animal" in order to accomplish Crohn's disease diagnosis. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The claims are drawn to a method for diagnosing Crohn's disease comprising steps of "taking a biological sample from an animal that developed or is associated with a risk of developing Crohn's disease" and "analyzing the expression of at least one gene selected from the group consisting of a gene of type 6 protein phosphatase regulated by interleukin 2, a gene of a Traf 2 and Nck interacting kinase, a gene of FLICE inhibitory protein and a gene of glucocorticoid receptor α, in the biological sample." Claim 11 further requires "analyzing the expression of at least one gene selected from the group consisting of a gene of cytochrome oxidase subunit I gene and a gene of cytochrome b," while claim 14 further requires that "the biological sample is an ileum tissue or colon tissue derived from an animal." It is noted that the instant specification clearly differentiates "expression of a gene" from "expression of a protein",

and teaches that analysis of expression of a gene refers to detection of gene transcripts/mRNA (see, e.g., pages 10-11, Examples 2-3, and, e.g., independent claim 10 as compared to independent claim 12). Accordingly, the claims as written do not encompass methods of protein/polypeptide detection.

The specification discloses that expression of the genes encoding type 6 protein phosphatase (PP6), Traf 2 and Nck interacting kinase (TNIK), FLICE inhibitory protein (FLIP), glucocorticoid receptor *α* (GR*α*), cytochrome oxidase subunit I, and cytochrome b is increased in samples of inflamed colon tissues and ileum tissues as compared to uninflamed tissues in human Crohn's disease patients (see entire specification, particularly Examples 1-2). The evidence provided in the specification does indicate that only subsets of this group of genes exhibit increased expression in some patients, and that the extent of the increase varies from patient to patient and in colon as compared to ileum (see, e.g., Table 2). However, the teachings of the specification are sufficient to enable those of skill in the art to practice methods of diagnosing Crohn's disease in which increased expression of one or more of the genes encoding PP6, TNIK, FLIP, and GR*α*, alone or in combination with the gene encoding cytochrome oxidase subunit I and/or cytochrome b is detected in a human colon tissue or ileum tissue sample, as increased expression of any of these genes/combinations in such samples is one factor that a skilled artisan would reasonably consider in diagnosing Crohn's disease, given the guidance provided in the specification. However, it is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims.

The instant claims are not limited to methods of diagnosing Crohn's disease in which increased expression of one or more of the genes encoding PP6, TNIK, FLIP, and GRα, alone or in combination with the gene encoding cytochrome oxidase subunit I and/or cytochrome b, is detected in a human colon or ileum tissue sample. Rather, the claims encompass methods in which the expression of one or more of these genes is "analyzed" in any manner, and methods in which any type of "biological sample" from any "animal" is employed. It is first noted that the prior art as exemplified by Engstrand (Scandinavian Journal of Infectious Disease 98 (Suppl):27-29 [1995]) discloses that Crohn's disease is known to those of skill in the art as a human disease (see entire reference, particularly page 27). While related conditions occur in other animals (e.g., Johne's disease, as disclosed by Engstrand at, e.g., page 27), such diseases are not known as "Crohn's disease." However, the instant specification clearly indicates at page 10 that the term "animal" means "various mammals inclusive of human and birds" and that "Examples thereof include human, monkey, dog, cat, cow, horse, pig, mouse, rabbit, chicken and the like." Accordingly, the claims as written encompass detection of Crohn's disease in animals other than humans. However, the specification provides no evidence of any association between expression of the genes of the claims and Crohn's disease in any non-human animal. Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for further guidance and enablement of a claimed invention. However, as discussed above the prior art teaches that Crohn's disease is a human disease, and the prior art does not provide any evidence that analysis of expression of any of the genes recited in the claims facilitates or enables

detection of Crohn's disease in a non-human animal. Accordingly, it is completely unpredictable as to whether one of skill in the art could practice the method of the claims using non-human samples. The instant claims are also sufficiently broad so as to encompass any method or manner of "analyzing the expression" of at least one of the genes of the claims. Thus, the claims as written encompass methods in which, e.g., the mere presence of a gene transcript is detected. However, the data presented in the specification makes clear that gene transcripts are present in both diseased and healthy tissues; it is the increased levels of expression in diseased tissues that indicates Crohn's disease (see entire specification, particularly Examples 1-2). Accordingly, while the teachings of the specification would enable one of skill to diagnose Crohn's disease by detecting the level of gene expression, it is apparent from the teachings of the specification that other methods of "analyzing" gene expression (e.g., detection of the mere presence of transcripts) would not be sufficient to achieve diagnosis. Further, the specification teaches at page 10 that the term "biological sample" encompasses any sample that permits detection of "noticeable changes in the expression" of the genes of the invention, and indicates that such samples may include "cell, tissue, urine, blood and the like." However, the data provided in applicant's specification is limited to results obtained with samples of colon tissues and ileum tissues (see Examples 1-3). While it is clearly within the ability of a skilled artisan to assay for differences in levels of gene expression in a variety of biological sample types (such as any of those listed in applicant's specification), the specification does not provide any evidence that differences in expression levels of the genes of the claims actually occur in patients

afflicted with Crohn's disease in sample types other than colon or ileum tissue. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of the invention. However, the prior art does not provide evidence of differences in expression of the genes/combinations of the claims in any type of biological sample from a Crohn's disease patient. The prior art as exemplified by Solis-Herruzo et al (Digestive Diseases and Sciences 38(9):1631-1637 [1993]) discloses that the concentration of cytochrome b in the membranes of circulating neutrophils is reduced in Crohn's disease patients as compared to healthy controls (see entire reference, particular page 1634). (It is again noted that the instant claims encompass detection of cytochrome b gene expression only in combination with one or more of the genes of claim 10; see claims 10-11). While Solis-Herruzo et al suggest that the observed altered cytochrome b levels may stem from a genetic defect (see page 1635), the reference does not provide evidence of the molecular basis of the disclosed difference in membrane protein levels, and it is well known to those of skill in the art that differences in the quantities of membrane proteins observed in a cell may arise for a variety of reasons (differences in transcription resulting from increased or decreased transcription factor levels, differences in translation, variations in mRNA stability or in transport of proteins into the membrane, etc). Further, to the extent that one might assume that membrane protein levels could serve as an indicator of mRNA/transcript levels, the decreased levels of cytochrome b observed by Solis-Herruzo et al in neutrophils suggest that the increased levels observed by applicant in colon/ileum cannot be considered indicative of transcript levels that might be observed

in other types of biological samples. Thus, the prior art does not provide additional guidance that would enable one of skill in the art to practice applicant's invention with different types of biological samples, or to practice applicant's invention using a manner of "analyzing" gene expression other than that enabled by the specification. Given the high level of skill of one of skill in the relevant art, it is clearly within the ability of such an artisan to conduct further experimentation in order to determine whether applicant's method may be employed successfully by detecting expression levels of the genes/combinations of the claims in other types of biological samples, and/or by performing other types of expression "analysis" on a biological sample. However, the outcome of such further research cannot be predicted, and, accordingly, it is unpredictable as to whether any quantity of experimentation would be sufficient to enable applicant's invention as now claimed. Accordingly, while the teachings of the specification enable methods of diagnosing Crohn's disease in which increased expression of at least one of the genes of claim 10 in a colon tissue sample or an ileum tissue sample of a human patient is detected as an indicator of Crohn's disease (alone or in combination with one or more of the genes of claim 11), it would require undue experimentation to use applicant's invention in a manner reasonably commensurate with the instant claims. With further regard to claim 14, it is noted that while the claim is limited to methods in which "the biological sample is an ileum tissue or colon tissue," the claim as written encompasses the use of samples from any "animal" and any manner of "analyzing" gene expression.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 10-11 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-11 and 14 are indefinite because it is unclear as to how the practice of the method steps of the claim would allow one to diagnose Crohn's disease. The claims are drawn to a method "for diagnosing Crohn's disease," but recite a final step that merely requires "analyzing the expression of at least one gene" of the claims in a biological sample. This language does not apprise one of skill in the art as to how analysis of gene expression would allow one to achieve disease diagnosis, and it is not clear from the language of the claims as to whether the claims are actually intended to be drawn to a method for "diagnosing Crohn's disease" or to a method for analyzing expression of a gene or genes in a biological sample. Clarification is required.

Claims 10-11 and 14 are indefinite over the recitation of the phrase "an animal that developed or is associated with a risk of developing Crohn's disease" in step (a) of claim 10. The teachings of the specification indicate that the method of the invention employs a biological sample taken from an animal that is a "target" of diagnosis, wherein when the expression of one of the genes of the claims is "high" the animal "is diagnosed as having developed Crohn's disease or having a high likelihood of developing Crohn's disease" (see page 10). However, the language of the claim as written seems to indicate that the method is to be performed on an animal that is known

to have Crohn's disease or an animal that is somehow "associated with a risk of developing Crohn's disease" (e.g., an animal who carries an infectious agent that might infect another animal and thereby cause Crohn's disease, etc.). Further, neither the specification nor the prior art make clear what might be considered to constitute an animal that is "associated with a risk of developing Crohn's disease." Thus it is unclear, based on the language of the claims, as to whether the claims are intended to be drawn to a method in which a sample is taken from an animal in order to determine whether that animal has Crohn's disease, or whether the method is to be practiced on animals having Crohn's disease or in some manner "associated with" Crohn's disease (and further as to what such animals might be). Clarification is required.

Claims 10-11 and 14 are indefinite over the recitation of the language "gene of type 6 protein phosphatase," "gene of a Traf 2 and Nck interacting kinase," "gene of FLICE inhibitory protein," and "gene of glucocorticoid receptor α" in claim 10, and claim 11 is further indefinite over the recitation of the language "gene of a cytochrome oxidase subunit I gene" and "gene of cytochrome b." It is unclear as to whether this language is intended to refer to genes that, e.g., encode the recited proteins (e.g., to a gene encoding type 6 protein phosphatase," etc.), or whether the language "gene of" a protein is intended to refer to a molecule that is "of" or obtained from a protein. Particularly, the recitation "gene of a cytochrome oxidase subunit I gene" in claim 10 suggests that applicant may intend to differentiate a "gene of" a gene from a "gene of" a protein. Clarification is required. This rejection could be overcome by amending the

claims to recite, e.g., "a gene encoding type 6 protein phosphatase," "a gene encoding cytochrome oxidase subunit I," etc.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 703/305-0761. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 703/308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are 703/872-9306 for regular communications and 703/872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703/308-0196.

Diana B. Johannsen
April 21, 2003